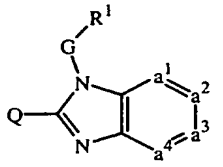
Claims

1. A compound of formula



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

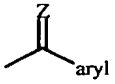
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

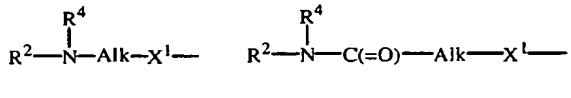
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)-aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

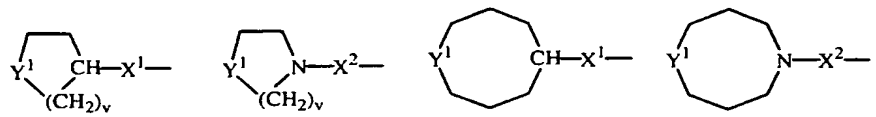


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1) (b-2) (b-3) (b-4)



(b-5) (b-6) (b-7) (b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;
t is 2, 3, 4 or 5;
u is 1, 2, 3, 4 or 5;
v is 2 or 3; and
whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;
G is C_{1-10}alkanediyl substituted with one or more hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, HO(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy-(-CH_2-CH_2-O)$_n$- or arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-;
R^1 is a monocyclic heterocycle or aryl; said heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;
each n independently is 1, 2, 3 or 4;
R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;
R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;
R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;
R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

2. A compound according to claim 1 wherein -a^1=a^2-a^3=a^4- is a radical of formula (a-1) or (a-2).

3. A compound according to claim 1 or 2 wherein R^1 is phenyl optionally substituted with halo, C_{1-6}alkyl or C_{1-4}alkyloxy; or pyridyl optionally substituted with 1 or more substituents selected from arylC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, mono-or di(C_{1-6}alkyl)amino, C(=O)-$NR^{5c}R^{5d}$, halo or C_{1-6}alkyl.

4. A compound according to any one of claims 1 to 3 wherein G is C_{1-4}alkanediyl substituted with hydroxy, C_{1-6}alkyloxy, HO(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- or arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-.

5. A compound according to any one of claims 1 to 4 wherein Q is a radical of formula (b-5) wherein v is 2 and Y^1 is -NR^2-.

6. A compound according to any one of claims 1 to 5 wherein X^1 is NH or CH_2.

7. A compound according to any one of claims 1 to 6 wherein R^2 is hydrogen or C_{1-10}alkyl susbstituted with NHR^6 wherein R^6 is hydrogen or C_{1-6}alkyloxycarbonyl.

8. A compound according to claim 1 wherein the compound is [(A),(S)]-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)-ethoxymethyl]-1*H*-benzimidazol-2-amine; [(A),(S)]-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine (compound 75); (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; *N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-4-methyl-1*H*-benzimidazol-2-amine trihydrochloride trihydrate; [(A),(R)]-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; [(A)(S)]-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-

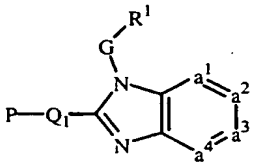
2-amine; [(A),(R)]-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-2-benzimidazol-2-amine; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; [(B),(S)] *N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-7-methyl-3*H*-imidazo[4,5-b]pyridin-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-phenyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-metyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-4-methyl-*1H*-benzimidazol-2-amine monohydrate; [(A),(R)]-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-*1H*-benzimidazol-2-amine;
a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof.

9. A compound as claimed in any one of claims 1 to 8 for use as a medicine.

10. A pharmaceutical compositioncomprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 8.

11. A process of preparing a composition as claimed in claim 10, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described in any one of claims 1 to 8.

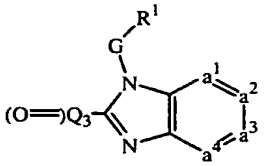
12. An intermediate of formula



(IV)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, P being a protective group, and Q_1 being defined as Q according to claim 1 provided that it is devoided of the R^2 or R^6 substituent.

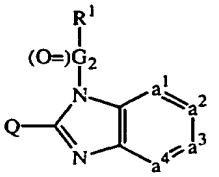
13. An intermediate of formula



(IX)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)Q_3$ being a carbonyl derivative of Q, said Q being defined according to claim 1, provided that it is devoided of the $-NR^2R^4$ or $-NR^2-$ substituent.

14. An intermediate of formula

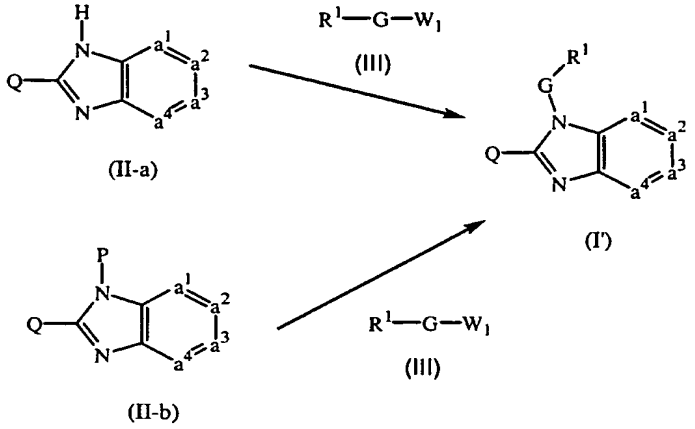


(XXII)

with R^1, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)G_2$ being a carbonyl derivative of G, said G being defined according to claim 1.

15. A process of preparing a compound as claimed in claim 1, characterized by,

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



(II-a)

(III)

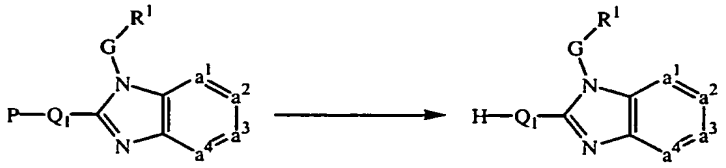
(I')

(II-b)

(III)

with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

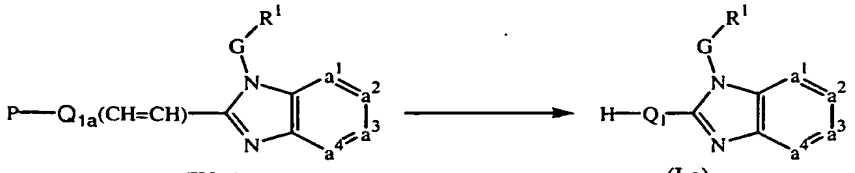
b) deprotecting an intermediate of formula (IV)



(IV) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

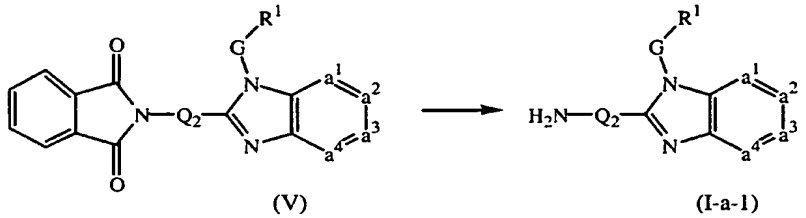
c) deprotecting and reducing an intermediate of formula (IV-a)



(IV-a) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, $Q_{1a}(CH=CH)$ being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group;

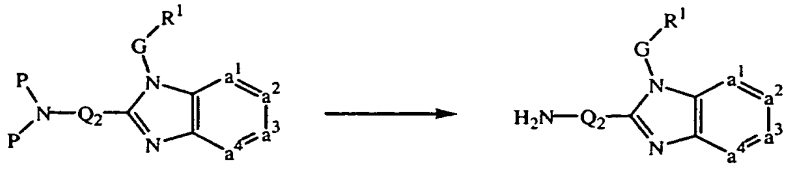
d) deprotecting an intermediate of formula (V)



(V) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

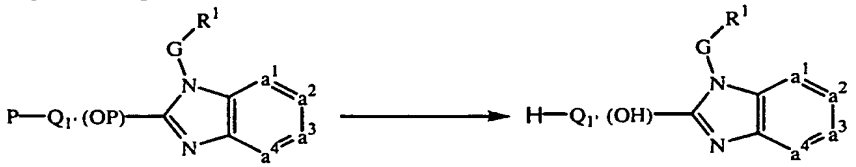
e) deprotecting an intermediate of formula (VI)



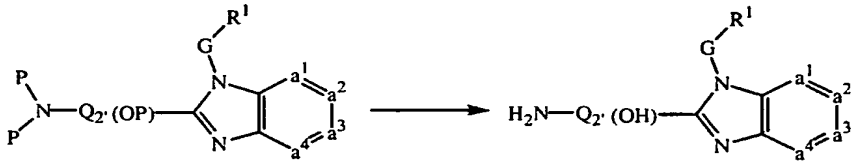
(VI) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)



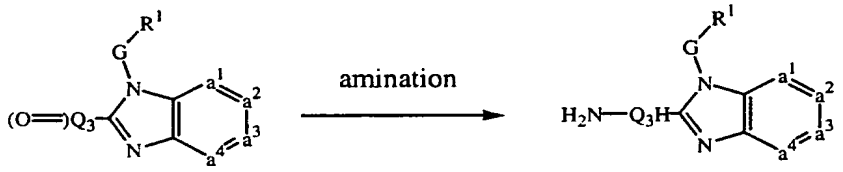
(VII) (I-a-2)



(VIII) (I-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H-Q_1\cdot(OH)$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_2\cdot(OH)$ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

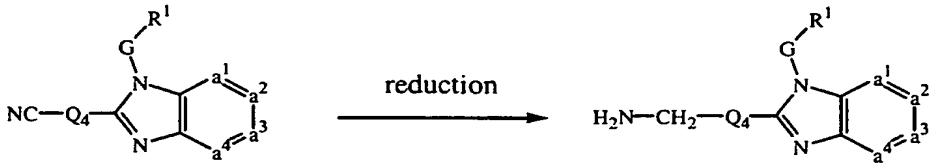
g) amination of an intermediate of formula (IX)



(IX) (I-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

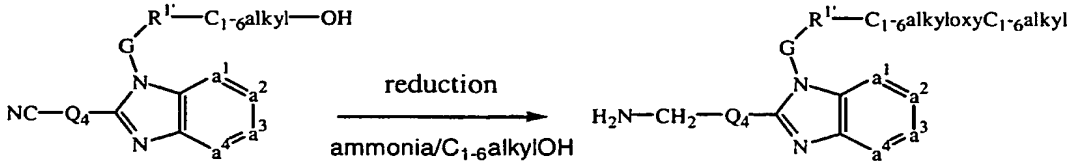
h) reducing an intermediate of formula (X)



(X) (I-a-1-3)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

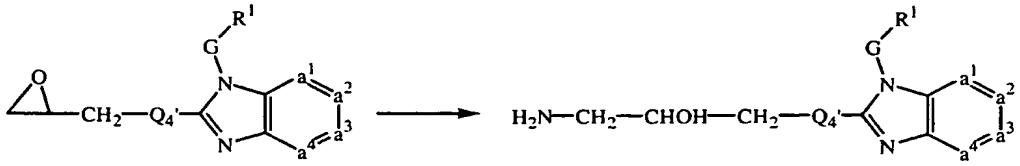
i) reducing an intermediate of formula (X-a)



(X-a) (I-a-1-3-1)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$ being defined as R^1 according to claim 1 provided that it comprises at least one substituent, in the presence of a suitable reducing agent and suitable solvent;

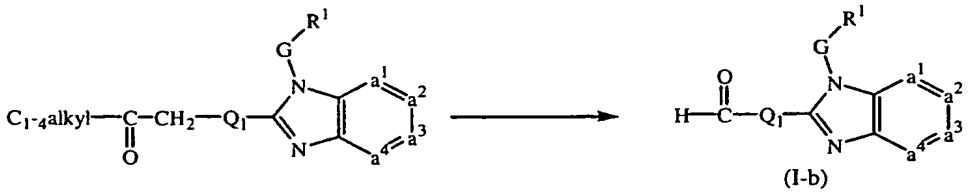
j) amination of an intermediate of formula (XI)



(XI) (I-a-1-3-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-CHOH-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of a suitable amination reagent;

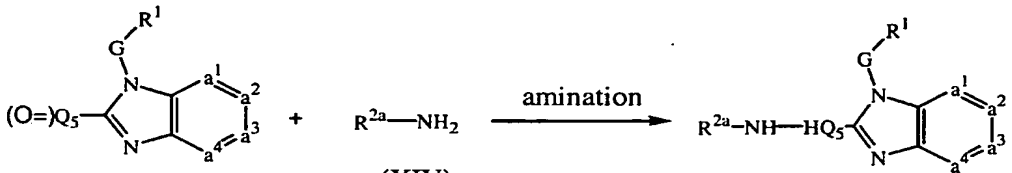
k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



(XII) (I-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-C(=O)-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is formyl;

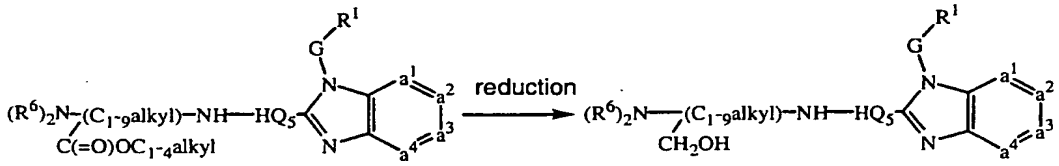
l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



(XIII) (XIV) (I-c)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and R^{2a}-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

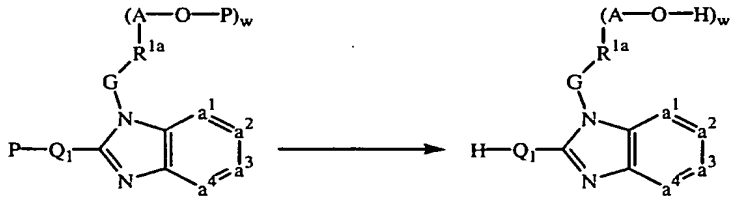
m) reducing an intermediate of formula (XV)



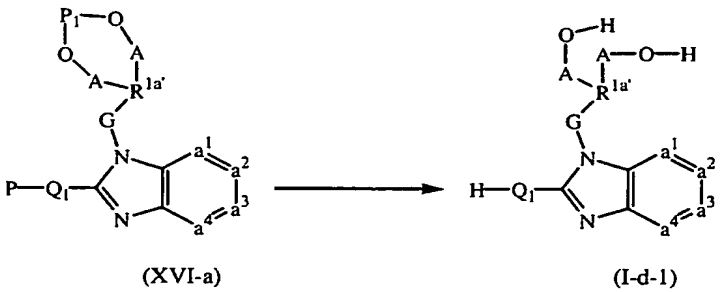
(XV) (I-c-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(R^6)_2N$-[$(C_{1-9}$alkyl)CH_2OH]-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

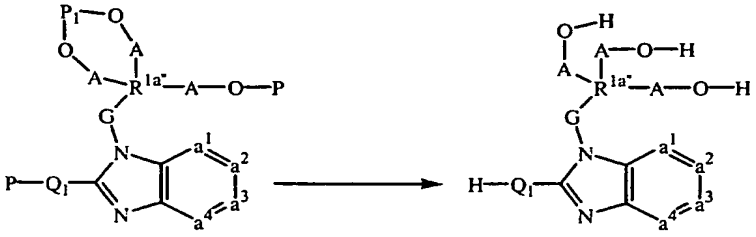
n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)



(XVI) (I-d)



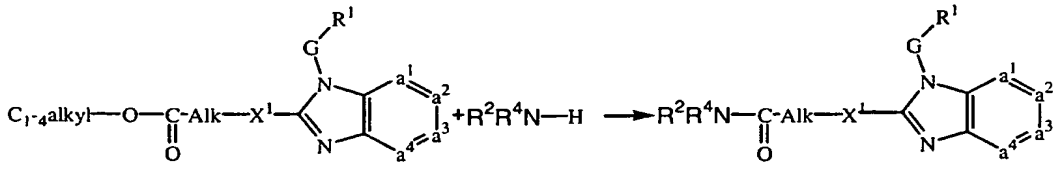
(XVI-a) (I-d-1)



(XVI-b) (I-d-2)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 1 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, with w being an integer from 1 to 4 and P or P_1 being a suitable protecting group, with a suitable acid.

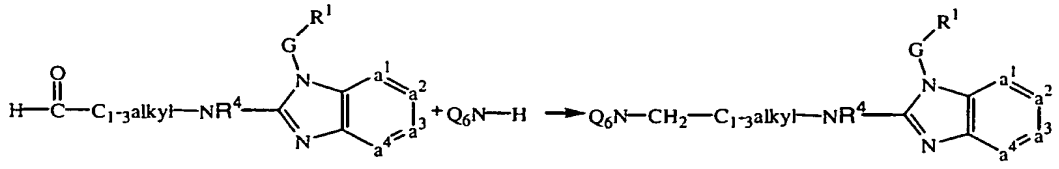
o) amination of an intermediate of formula (XVII)



(XVII) (XVIII) (I-e)

with R^1, G, $-a^1=a^2-a^3=a^4-$, Alk, X^1 R^2 and R^4 defined as in claim 1, in the presence of a suitable amination agent;

p) amination of an intermediate of formula (XIX)

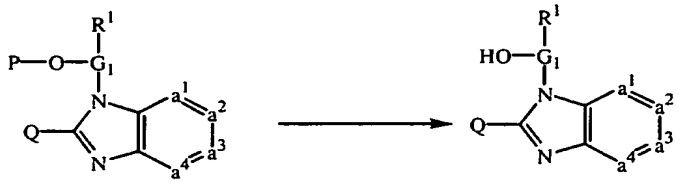


(XIX) (XX) (I-p)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and Q_6N-CH_2-C_{1-3}alkyl-NR^4

being defined as Q according to claim 1 provided that in the definition of Q, X^2 is C_{2-4}alkyl-NR^4, in the presence of a suitable amination agent;

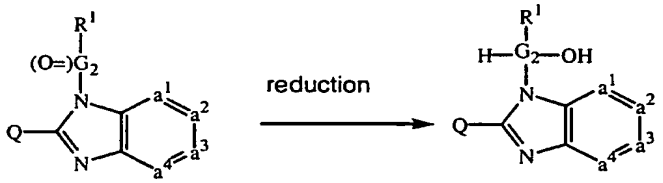
q) deprotecting an intermediate of formula (XXI)



(XXI) (I-q)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and HO-G_1 being defined as G according to claim 1 provided that G is substituted with hydroxy or HO-$(CH_2CH_2O-)_n$;

r) reducing an intermediate of formula (XXII)



(XXII) (I-q-1)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-G_2-OH being defined as G according to claim 1 provided that G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a suitable reducing agent.

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, metal complexes, quaternary amines or *N*-oxide forms thereof.

16. A product containing (a) a compound as defined in claim 1, and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment or the prevention of viral infections.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound as defined in claim 1, and (b) another antiviral compound.